

Correspondence

ANALYSIS OF IgE-BINDING ALLERGENS IN *CULEX QUINQUEFASCIATUS* SALIVA PROTEIN IN MOSQUITO BITE ALLERGIC PATIENTS

To the Editor:

Specific IgE antibodies to *Culex quinquefasciatus* have been identified in human sera by immunoblot techniques using whole-body extract and salivary gland extract.^{1,2} However, the cases reported in this research occurred in residents of countries where *C quinquefasciatus* is less prevalent as a human-biting species. Still no reports have dealt with *C quinquefasciatus* pure saliva proteins and their specific IgE responses. Because saliva components of mosquito cause allergy,³ we aimed to identify the allergenic components of pure saliva proteins of *C quinquefasciatus* and their IgE-binding fragments in mosquito bite allergic patients who live in Thailand, where *C quinquefasciatus* is a prevalent human-biting species.

Serum samples were obtained from 69 adult and children outpatients of the Department of Dermatology and the Department of Pediatrics at Siriraj Hospital with clinical manifestation of either immediate or delayed or both immediate and delayed skin reaction. Diagnosis of insect bite allergy in these patients was based largely on their skin lesion definition of insect bite reaction⁴ and on a previous history of insect bite allergy. Twenty nonallergic individuals with no history of allergy who had normal IgE levels at the time of blood collection were used as controls. Saliva extract were collected from females of *C quinquefasciatus* using the Boorman method.⁵ All study participants were tested for *C quinquefasciatus* saliva specific IgE antibodies by an enhanced chemiluminescence immunoblot technique.

Figure 1 shows the specific IgE antibodies response patterns in study participants. High percentages of IgE response to saliva allergens with a molecular weight higher than 37 kDa were found in both allergic and nonallergic participants.

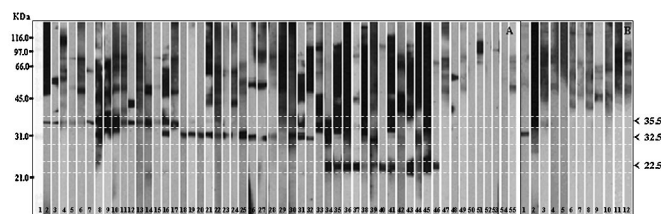


Figure 1. IgE responses to saliva allergens of *Culex quinquefasciatus* in study participants. A, Lane 1, molecular weight marker; lanes 2 to 55, 54 patients allergic to mosquitoes; B, Lanes 1 to 5, representative of patients allergic to other insects; lanes 6 to 12, representative of nonallergic study participants. The 35.5-, 32.5-, and 22.5-kDa specific saliva allergens are indicated by arrows.

The presence of anti-mosquito saliva antibodies in almost all examined study participants is not unexpected, because *C quinquefasciatus* is common in Thailand and every person is frequently bitten by this mosquito from early childhood. Nevertheless, specific IgE response to 35.5-, 32.5-, and 22.5-kDa allergens of *C quinquefasciatus* saliva occurred only in allergic patients in this study. The IgE antibodies against 35.5-, 32.5-, and 22.5-kDa allergen bands were found in 22 (41%), 15 (28%), and 13 (24%) of 54 allergic patients with a history of mosquito bite allergy, respectively. IgE antibodies against 22.5 kDa were found mainly in allergic children (13/19) with a history of mosquito bite. If the 3 saliva allergens identified in this research are cloned and prepared as cocktail allergen, the allergen will significantly improve diagnosis of mosquito bite allergy and improve specific immunotherapy for patients with systemic reactions to mosquito bites.

The 35.5- and 32.5-kDa allergens were also found in 4 (24%) and 3 (20%) of 15 allergic patients with a history of other insect bite allergy successively. This result indicates that the saliva of *C quinquefasciatus* may contain shared allergens with other insects, since cross-reactivity between mosquito saliva allergens and allergens from other biting insects and crustaceans has been reported previously.^{3,6}

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REFERENCES

1. Peng Z, Li H, Simons FE. Immunoblot analysis of salivary allergens in 10 mosquito species with worldwide distribution and the human IgE responses to these allergens. *J Allergy Clin Immunol*. 1998;101(4 pt 1):498–505.
2. Jeon SH, Park JW, Lee BH. Characterization of human IgE and mouse IgG1 responses to allergens in three mosquito species by immunoblotting and ELISA. *Int Arch Allergy Immunol*. 2001;126:206–212.
3. Peng ZF, Simons FR. Mosquito allergy: immune mechanisms an recombinant salivary allergens. *Int Arch Allergy Immunol*. 2004;133:198–209.
4. Peng Z, Yang M, Simons FE. Immunologic mechanisms in mosquito allergy correlation of skin reactions with specific IgE and IgG antibodies and lymphocyte proliferation response to mosquito antigens. *Ann Allergy Asthma Immunol*. 1996;77:238–244.
5. Boorman J. Induction of salivation in biting midges and mosquitoes, and demonstration of virus in the saliva of infected insects. *Med Vet Entomol*. 1987;1:211–214.
6. Martinez-Molero MI. Urticaria caused by arthropod bites and stings (excluding Hymenoptera). *Allergol Immunopathol*. 1999;27:96–104.

SERUM SICKNESS-LIKE REACTIONS AFTER PLACEMENT OF SIROLIMUS-ELUTING STENTS

To the Editor:

The use of drug-eluting stents (DESs) for the treatment of coronary artery disease (CAD) is rapidly increasing, with DESs accounting for more than 75% of all stents used.¹ Hypersensitivity reactions thought to be related to the stent itself have occasionally been reported, ranging from mild rash to anaphylaxis, including some fatal reactions, as discussed in a recent review.² Therefore, allergists may be asked to evaluate hypersensitivity reactions that may occur in the poststenting period. We report 2 cases of serum sickness-like reactions thought to be related to sirolimus-eluting stents.

Patient 1 was a 78-year-old man with CAD who underwent cardiac catheterization with placement of 3 sirolimus-eluting stents. He developed urticaria-like rash, myalgias, and arthralgias 18 days after placement of the stents. Use of clopidogrel was discontinued and ticlopidine was substituted, but symptoms did not resolve. Pertinent laboratory measurements are given in Table 1. Symptoms resolved with prednisone. Symptoms relapsed briefly after the prednisone, but 1 month after stent placement the patient was symptom free.

Table 1. Pertinent Laboratory Measures

Component	Patient 1	Patient 2	Reference range
WBC, $\times 10^3/\mu\text{L}$	10.4	17.0	4–11
Differential, %	81 PMNs	91 PMNs	50–70
Platelets, $\times 10^3/\mu\text{L}$	244	273	150–440
ESR, mm/h	57	120	0–20

Abbreviations: ESR, erythrocyte sedimentation rate; PMNs, polymorphonuclear leukocytes; WBC, white blood cells.

Patient 2 was a 54-year-old woman with CAD who underwent placement of 2 sirolimus-eluting stents. She developed urticaria-like rash, arthralgias, and arthritis 17 days after her procedure. Pertinent laboratory measurements are given in Table 1. The symptoms resolved with prednisone, and 1 month after stenting the patient was symptom free. The patient started taking aspirin and clopidogrel at the time of the stenting. After the serum sickness-like reaction had resolved, she continued taking aspirin and clopidogrel without problem.

We describe 2 patients who developed atypical serum sickness-like reactions approximately 17 days after placement of sirolimus-eluting stents, which did not appear to be related to concomitant mediations. The inactive ingredients in the sirolimus-eluting stent are Parylene C and 2 polymers: polyethylene-covinyl acetate and poly n-butyl methacrylate, which enable the slow elution of sirolimus throughout approximately 30 days.³ In both of our cases, the reactions had subsided approximately 30 days after stent placement, supporting our impression that the hypersensitivity reactions were due to either the sirolimus or the eluting polymer.

A variety of hypersensitivity reactions to DESs have been reported,² but to our knowledge this is the first report of patients with symptoms consistent with serum sickness-like reactions that closely followed the 30-day course of release of sirolimus. A recent editorial suggested that DES reactions could be due to the polymer rather than sirolimus itself, but this has not been proven.⁴ The possibility of such reactions to the polymer vs the sirolimus itself should be considered when patients present with hypersensitivity symptoms in the post-catheterization period. Often, such reactions are blamed on new thienopyridine medications such as clopidogrel or ticlopidine, but this may sometimes be erroneous. Prematurely stopping thienopyridine therapy after stent implantation has been shown to be strongly associated with subsequent mortality.⁵ Allergists should be familiar with the clinical presentation of these hypersensitivity reactions, and the possible causes should be carefully considered before taking action.

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REFERENCES

1. Mueller T. *Stories of Survival and Hope Mark the One Million Patient Milestone for the CYPHER Sirolimus-Eluting Coronary Stent*. Miami Lakes, FL: COMTEX; 2005.
2. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and

Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175–181.

3. *Instructions for Use: Cypher Sirolimus-Eluting Coronary Stent*. Miami Lakes, FL: Cordis Corp; 2006.
4. Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents: is it the pill or the polymer? *J Am Coll Cardiol*. 2006;47:182–183.
5. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113:2803–2809.

INVOLVEMENT OF LIPID TRANSFER PROTEIN IN ONION ALLERGY

To the Editor:

Hypersensitivity to onion has been described as a cause of contact dermatitis, rhinoconjunctivitis, and asthma induced by handling of onions, but few publications in the literature report allergic reactions due to onion ingestion despite its wide use.¹ Herein, we describe a case of a 19-year-old atopic woman who experienced urticaria after ingestion of raw onions. The patient had had rhinoconjunctivitis and contact urticaria to mugwort for the past 2 years, and oral pruritus after ingestion of raw onion and peel peach had occurred 1 year ago.

Skin prick testing with commercial extracts was performed with a battery of plant food and pollen allergens (ALK-Abelló S.A., Madrid, Spain). The presence of IgE specific serum antibodies to onion, peach, and mugwort pollen was investigated with the CAP-FEIA system (Phadia AB, Uppsala, Sweden). In addition, the ADVIA-Centaur platform (Bayer Corporation, Tarrytown, NY) was used to detect serum IgE to natural (n) or recombinant (r) forms of some purified allergens: nArt v 1, rPru p 3 (peach lipid transfer protein [LTP]), and rMal d 4 (apple profilin). IgE cross-reactivity studies were performed by means of immunoblotting inhibition with nArt v 3 (mugwort LTP) and rPru p 3 as inhibitors.

Skin prick test results were positive for mugwort, grass, olive, and chenopodium pollen extracts and for onion, peach, and tomato extracts. Serum specific IgE test results were positive to onion (5.41 kU/L), peach (18 kU/L), mugwort (0.86 kU/L), and Pru p 3 (23.07 kU/L) and were negative to Mal d 4 and Art v 1. IgE immunoblotting of onion extract (obtained by magnetic stirring with 1.8% sodium chloride) only revealed a 12-kDa IgE-binding protein band. No IgE binding to Art v 3 was detected. The IgE binding to the 12-kDa onion band was inhibited by onion extract and rPru p 3 but not by nArt v 3.

The onions belongs to the Liliaceae family, as do asparagus, garlic, and leek. Although cross-reactivity among members of this family has not been reported,² an IgE-binding band of 12 kDa had been found in young garlic (maybe an LTP),³ and allergenic LTP has been described in asparagus.⁴ In a study by Asero et al,¹ an onion IgE-binding, 15-kDa protein was found, and preabsorption of the patient's serum with peach LTP caused the total loss of this onion protein;

nevertheless, the authors considered another 43-kDa protein as the relevant allergen.

Recently, 2 patterns of plant food allergy across Europe have been described. In North and Central Europe, food allergy is preceded by birch pollen allergy, and the main food allergen involved is homologous to Bet v 1, whereas in South Europe food allergy is severe and the main allergen is an LTP.⁵ Furthermore, mugwort LTP has been suggested as a primary sensitizing agent in patients with mugwort pollinosis and plant food allergy due to LTPs.⁶

This case report confirms LTP as a relevant allergen in onion food allergy and emphasizes the difficulties in establishing the sensitization pathway in patients with food allergy due to LTP. On the one hand, in this case the clinical history suggests mugwort LTP as the primary sensitizing agent, but on the other hand, laboratory results indicated that mugwort pollinosis was an independent phenomenon to onion and peach food allergy.

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REFERENCES

1. Asero R, Mistrello G, Roncarolo D, Amato S. A case of onion allergy. *J Allergy Clin Immunol*. 2001;108:309–310.
2. Sánchez-Hernández MC, Hernández M, Delgado J, et al. Allergic cross-reactivity in the Liliaceae family. *Allergy*. 2000;55:297–299.
3. Pérez-Pimiento AJ, Moneo I, Santaolalla M, de Paz S, Fernández-Parra B, Domínguez-Lázaro AR. Anaphylactic reaction to young garlic. *Allergy*. 1999;54:626–629.
4. Díaz-Perales A, Tabar AI, Sánchez-Monge R, et al. Characterization of asparagus allergens: a relevant role of lipid transfer proteins. *J Allergy Clin Immunol*. 2002;110:790–796.
5. Fernández-Rivas M, Bolhaar S, González-Mancebo E, et al. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant food. *J Allergy Clin Immunol*. 2006;118:481–488.
6. Lombardero M, García-Sellés FJ, Polo F, et al. Prevalence of sensitization to Artemisia allergens Art v 1, Art v 3 and Art v 60 kDa: cross-reactivity among Art v 3 and other relevant lipid-transfer protein allergens. *Clin Exp Allergy*. 2004;1415–1421.

WOULD ORAL DESENSITIZATION FOR PEANUT ALLERGY BE SAFER THAN AVOIDANCE?

To the Editor:

I write to support the letter from Dr Mansfield in the August issue of the *Annals*¹ that drew attention to the devastating effect of peanut allergy on the family and how oral desensitization can be a practical alternative to avoidance. This is far from a new idea; in 1908, Dr Schofield from London, England, reported in the *Lancet*² how he successfully desensitized a boy who was dangerously allergic to egg by giving him pills that contained gradually increasing amounts of egg, while avoiding egg completely. The starting dose was 1/10,000 of an egg, the results of a challenge test were negative after 6 months, and thereafter the boy could eat an egg every day. It is really remarkable that this treatment was performed in 1906, the same year that Von Pirquet coined the word *allergy*.

In 1985, at the American Academy of Allergy, Asthma and Immunology meeting in New York,³ John W. Gerrard reported on 6 cases of peanut allergy desensitized by the oral route. I was present on that day and recall how severely he was criticized for giving such dangerous treatment. In 2004, Meglio et al⁴ successfully desensitized 15 of 21 children proven by double-blind, placebo-controlled challenge to be severely milk allergic. After the initial stages, this treatment was performed at home without problems. Three children could not be completely desensitized, but because they could tolerate small amounts of milk they were no longer in danger.

John Freeman, who was the first to use subcutaneous immunotherapy in 1911,⁵ taught many thousands of patients how to give themselves grass pollen injections safely every day for 54 days with excellent results. Every spring until 1959 up to 6,000 patients attended the Allergy Clinic at St Mary's Hospital in London to receive their aqueous vaccine kits and meticulous instruction in self-inoculation. Although the top dose of 1.0 mL of 10% (wt/vol) aqueous grass pollen extract was high and the final objective was a negative skin test result to grass pollen, the daily increase in dose was gradual and no serious incidents were ever encountered (A. W. Frankland, personal communication, July 2006).

Freeman, who coined the term *rush desensitization*, stated in his annual report to the British Asthma Research Council in 1938, "Rush treatment has given dramatic results. We remember a cow-herd who was said by his noble patron to look like a cow, think like a cow, and sometimes speak like a cow. He had no interest in life beyond his beloved animals, yet whenever he went near them he got fearful attacks of eczema and asthma. He sat in his cottage all day mourning his exile from the cow-shed, but after five days of a rush desen-

sitization he could milk cows without the slightest trouble." Could we achieve that result today?

Complete avoidance of the causative food is the standard medical advice today, but this is a policy that places the main responsibility for avoidance on the parents and child, who is left vulnerable to unintentional ingestion and anaphylaxis. Must we condemn more and more children and some adults to live in constant fear of a dangerous reaction and therefore required to carry epinephrine autoinjectors, with inevitable disruption of the quality of life of the whole family? Surely there must be a better alternative, such as inducing tolerance by gradual reintroduction of the causative food, as recently reviewed by Niggemann et al.⁶

I suggest that the uncontrollable danger presented by unintentional ingestion of an unknown amount of peanut should be compared with the controllable risk of oral or sublingual desensitization, using appropriate dilutions of standardized peanut extracts. A trial of this method must take great care to establish a starting dose below the threshold of reaction, thereafter increasing the daily dose gradually to avoid reactions and allow ample time for tolerance to be acquired. Meticulous instruction and collaboration with carefully selected families would be essential. I am certain that many would prefer to take an active part in treatment rather than live in constant fear of anaphylaxis.

A clinical trial of oral or sublingual induction of specific tolerance to peanut or other foods could demonstrate a practical answer to an increasingly common problem. If complete desensitization to egg could be accomplished a hundred years ago, it should be possible to repeat this successful treatment today, provided that the regulatory requirements are satisfied. But can we turn back the clock?

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REFERENCES

1. Mansfield L. Successful oral desensitisation for systemic peanut allergy. *Ann Allergy Clin Immunol.* 2006;97:266.
2. Schofield AT. A case of egg poisoning. *Lancet.* 1908;1:716.
3. Shenassa MM, Perelmutter L, Gerrard JW. Desensitisation to peanut [abstract]. *J Allergy Clin Immunol.* 1985;75:177.
4. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitisation in children with IgE mediated cow's milk allergy. *Allergy.* 2004;59:980-987.
5. Freeman J, Noon L. Further observations on the treatment of hay fever by hypodermic inoculation of pollen vaccine. *Lancet.* 1911;2:814-8166.
6. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer C. Specific oral tolerance induction in food allergy. *Allergy.* 2006; 61:808-811.